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GENETIC EPIDEMIOLOGY OF LESCH-NYHAN DISEASE

To the Editor: Lesch-Nyhan disease is rare, and its diagnosis is best confirmed by HPRT assay in one of a few research laboratories. This creates ascertainment problems which must be considered in any attempt at genetic epidemiology. We draw attention to such problems in a recent paper by Francke et al. [1] in a constructive spirit, for those proposing similar studies of uncommon biochemical disorders.

The first problem is in specifying what families are referred by clinicians to specialized laboratories. The 47 kindreds in the Francke report appear to be a subset of 148 families known to Seegmiller [2] and Nyhan. It is generally agreed that when the mode of inheritance is not fully established, patients with affected relatives are more likely to be referred to specialized centers dealing with inherited diseases than when they have a negative family history. Compulsive self-destructive behavior is the most striking but inconsistent presenting system, and problems of clinical diagnosis have been stressed [2, 3]. Death during the first decade is common, and many affected (especially isolated cases) must die undiagnosed. Clearly the probability of at least one living patient with pathognomonic symptoms increases with the number of affected in a pedigree. As for the number of probands in the population represented, a minimal incidence of 5.2 per million male births [4] corresponds to an ascertainment probability (π) of .075. The argument of the authors for a high ascertainment probability rests on an erroneously expected ratio of 2:1 which should be 4:1 (equation (20) in reference [5]). Overestimating π underestimates the proportion of sporadic cases [6].

A second problem is that two of the tests for heterozygous carriers, selection (S) and radioautography (R), appear to be unreliable. They give a backcross segregation frequency of 22 "carriers" to 0 normals ($\chi^2_1 = 22.0$), whereas other methods (cloning and hair follicle analysis) give a 39:37 backcross frequency (table 1). The significant excess of carriers is entirely accounted for by unreliable methods which can be detected by blind laboratory tests with suitable controls or failing that by segregation analysis, which here as elsewhere demonstrates its power to resolve ascertainment and diagnostic problems from genetic phenomena.

A third problem is associated with paternal age comparisons, which are best done with intrapedigree controls. The control value of 32.2 years for paternal grandfathers found by Barrai et al. [7] is close to the mean for Lesch-Nyhan mutant carriers. In large studies, no effect of age on sex-linked mutants has been demonstrated, although two much smaller studies, one unpublished and the other with controls from the general population, claim significance [6].

If either sex has an age effect on the mutation rate, its average rate is not necessarily greater than the opposite sex, depending on the distribution of effects and ages at reproduction. Haldane [8] showed that at equilibrium between mutation and selection the sex ratio of the mutation rates is $w = m/x - 2$, where m is the selection coefficient

TABLE 1

Segregation Analysis of Lesch-Nyhan Disease

Group	Equation No. from [5]	Sample	U	K
A	(20)	An ancestral proband in sibship ($\hat{\pi} = .075$)	-1.05	100
	(4)	Not so; a carrier	2.00	180
	(4)	Not so; an affected brother	4.00	24
B	(4)	Carrier mother by C or H test	12.00	24
	(4)	Carrier mother by S or R test	32.00	64
C	. . .*	Mothers of isolated cases	-30.76	107
	(20), (71)	Segregation analysis of males	-14.24	63
D	. . .	Mothers of carrier mothers	-4.00	48
	. . .*	Mothers of isolated cases	3.95	4
	(71)	Brothers of carrier grandmother	1.08	10
	(70), (71)	Segregation analysis of males	4.49	36

Note.—Group A = women classified by C or H test and scored for $p = 1/2$; group B = women classified by S or R test and scored for $p = 1/2$; group C gives scores for $x = 1/3$; group D gives scores for $x' = 1/2$. U is a maximum likelihood score and K is its variance. In large-sample theory $(\Sigma U)^2/\Sigma K$ is distributed as χ^2_1 under H_0.

*$P(\text{noncarrier}|r = a = 1) = x/\{x + (1 - x)(1 - p)^b[x' + (1 - x')(1 - p)^u]\}$, where b is the number of brothers in the sibship and u is the number of maternal uncles [14].

against affected males, and x is the proportion of sporadic cases estimated from segregation analysis (along with the ancillary parameters p, x', and π) [9]. On the null hypothesis that $w = 1$, we have $x = m/3$, and the maximum likelihood score U_x may be transformed into $U_w = -m U_x/9$. The three sex-linked detrimentals are compared in table 2. Duchenne muscular dystrophy and hemophilia give an estimate of $w = .85 \pm .25$, corresponding to a nonsignificantly lower mutation rate in sperm than in eggs. Lesch-Nyhan disease, on the contrary, gives a higher estimate of $w = 3.59 \pm .87$ even when segregation analysis of males is omitted. Heterogeneity between the two bodies of data is highly significant ($\chi^2_1 = 9.13$). Either the Lesch-Nyhan data are biased by selective referral of familial cases, or some sex-linked loci show a sex difference in mutation rate and others do not. Carrier detection for Lesch-Nyhan disease contributes less than 8% of the information about w, and so the pooled estimate is only $w = 1.06 \pm .24$, in excellent agreement with an equal mutation rate in sperm and eggs.

On this evidence judgment should be suspended until a systematic survey can be made for Lesch-Nyhan disease. The present literature perpetuates rather than dispels inconsistency due to ascertainment problems. For both hemophilia [10] and Duchenne muscular dystrophy [11], a deficiency of sporadic cases has been claimed in studies which devote no attention to ascertainment problems or the necessity for blind testing of possible carriers and controls. Early in the history of this question a reduced circulation time was claimed (apparently without blind tests) which has not been confirmed [12]. A recent claim that nearly all mothers of Duchenne muscular dystrophy can be detected as carriers [11] differs from other experience and suggests inadequate controls. Meanwhile genetic studies continue to show a high frequency of sporadic cases [13].

In summary, the problems arising from biased ascertainment of rare biochemical diseases cannot be resolved merely by collecting larger samples. Valid inference requires an exceptionally intense and enlightened interest by biochemists in the

TABLE 2

INFORMATION ABOUT w, THE RATIO OF MUTATION RATES IN SPERM AND EGGS, ON THE NULL HYPOTHESIS ($w = 1$)

Sex-Linked Disease	Reference	Selection Coefficient (m)	Frequency of Sporadic Cases (x)	ML Score (u_w)	ML Information (K_{ww})	$U_w{}^2/K_{ww}$
Duchenne muscular dystrophy	[14]	.962	.32	−1.57	4.80	0.51
Hemophilia (A + B)	[15]	.750	.24	−0.03	1.92	0.00
	[7]	.620	.21	−0.79	9.46	0.07
Lesch-Nyhan	[1]	1.000	.33	3.42	1.32	8.84
Total	...	...	...	1.03	17.50	0.06

ascertainment of referred cases and the appropriate use of segregation analysis and blind clinical tests, without which even a registry with impeccable laboratory data would be as worthless as the Eugenics Records Office for epidemiological study.

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ANSWER TO CRITICISM OF MORTON AND LALOUEL

To the Editor: We recently reported on the occurrence of new mutants in X-linked recessive Lesch-Nyhan disease [1]. The emphasis of our paper was to point out the